Editorial

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Practicing Safe Modeling: GLP For Biologically Based Mechanistic Models

Risk assessment, as a discipline, includes such diverse research areas as stochastic modeling, physiology, and political science. Risk assessment has been characterized as pan-science, trans-science, pseudo-science, and voodoo-science. It is certainly controversial and complicated, requiring bench scientists to understand mathematical and statistical concepts and statisticians and mathematicians to understand and synthesize diverse areas of biology, physics, and law; it also places policy analysts in the unenviable position of trying to understand what the two groups have concluded. In many cases, the conclusions are delivered in multiple arenas, often yielding opinions that are contradictory.

From our point of view, risk assessment is one of the most challenging problems facing the scientific community. In essence, it requires that we aid regulators in the application of our findings on the health effects of xenobiotics to population exposures. There is a constant learning process in a broad spectrum of disciplines that challenges our creativity, intelligence, and overall diligence in a way which is seldom encountered in modern science. The areas of hazard assessment and dose–response analysis form the scientific kernel of risk assessment on the health effects of xenobiotics and continue to be areas of development and controversy.

A growing trend in the risk assessment community is the use of biologically based mechanistic models (BBMM) for dose–response analysis. The basic goal in using a BBMM is to describe the underlying biology of a toxicity in a mathematical or quantitative form that mimics reality as closely as possible. There is general belief that if the analysis is based upon a model with some biological underpinning, it will provide better risk estimates than an empirical model. This is true, provided one has applied "good laboratory practice" (GLP) to the development and application of a BBMM. What is "good laboratory practice" in biostatistics and biomathematics? How can one implement GLP when developing a BBMM? Our concept of GLP for BBMMs encompasses both biological and statistical concerns. All forms of mathematical analysis, from the calculation of simple means to the development of a complex model of endocrine feedback, are derived from a collection of assumptions or axioms. These assumptions govern the formula for the mean response in the population, the statistical distributions from which the data are assumed to arise, and the proper methods for parameter estimation. Assumptions in the development of a model may be biological or purely mathematical. Often one makes assumptions that are known to be biologically unrealistic to allow for mathematical tractability (e.g., cells are assumed to act independently of each other in the usual two-stage model of carcinogenesis), assumptions that concern the statistical noise in the data (e.g., data derived from a normal distribution), and assumptions about the qualitative form of the model (e.g., which metabolic pathways to include in a toxicokinetic model and which to exclude).

As the models become more complicated and the practitioners come from disciplines other than the traditional modeling fields of biostatistics and biomathematics, it is likely that these underlying assumptions will be ignored or misunderstood. This is of great concern because there are numerous publications illustrating the impact of slight changes in the assumptions used to develop a biomathemati-

cal model on the predictions derived from the model. The key to GLP in using models to analyze biological data is to understand the mathematical and statistical assumptions that go into the development of the model in order to assess the adequacy of those assumptions for the biological setting. The level of belief in the combination of assumptions used to derive and apply a model to a given biological problem will greatly determine the perceived quality of the prediction from the model. To blindly apply a BBMM to a given problem without an objective understanding of the assumptions being used is not likely to yield improved estimates of risk.

As the risk assessment community proceeds toward greater acceptance of BBMMs in the estimation of risks from environmental exposures, it is critical that criteria be developed for GLP in the application and development of BBMMs. Guidelines need to be established for such critical issues as objective methods of parameter estimation, inclusion and exclusion of data, the impact of varying assumptions, the consideration of alternative mechanisms, and the use of validation experiments. These guidelines can be developed to focus on specific biological and/or mathematical issues. Establishing these guidelines will provide an objective mechanism for judging BBMMs and will guide the research community in using the best possible means to obtain risk estimates from BBMMs. Adherence to such guidelines would also lead toward agreement between the various disciplines on the implications of mechanistically derived risk estimates.

One important way in which guidelines can be implemented is through the use of standard biomathematical and statistical computing packages in the analysis. Biomathematical packages such as ScOP and MatLab provide excellent tools for model simulation coupled with the basic tools needed for parameter estimation from most data situations. Statistical computing packages such as SAS provide a broad range of statistical tools for testing hypotheses and estimating variance with some basic tools for model formulation and development. However, neither of these types of computer packages were developed for the specific needs of the risk assessment community. If new computer packages or modules for the existing packages could be developed to insure the use of GLPs in the analysis, the acceptance and use of a BBMM in a risk assessment could be simpler and clearer.

The use of biologically based mechanistic models for dose–response analysis in risk assessment may prove to be a two-edged sword. This class of models has the potential to link diverse types of data in a biologically meaningful fashion to estimate low-dose risks. When done properly, these estimated risks should prove to be more reliable than those based upon empirical analyses of single data sets. However, use of these modeling techniques implies that the scientific and regulatory community will be faced with increasingly complicated analyses of risks from exposure to xenobiotics. Insuring that an analysis such as this conforms to the underlying biology (as well as sound statistical rules) will be a difficult task, especially when the underlying assumptions used to develop the model and estimate model parameters are misunderstood or simply ignored. Using GLP in model development and application should alleviate this problem.

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